Rare Diseases Clinical Research Network

Multicenter study to evaluate safety of fresolimumab in adults with moderate-to-severe Osteogenesis Imperfecta

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1. Protocol Synopsis

Protocol Number:	7706
Protocol Title:	Multicenter study to evaluate safety of fresolimumab in adults with moderate-to-severe osteogenesis imperfecta
Study Chair:	Brendan Lee, M.D.; Sandesh Nagamani, M.D.; V. Reid Sutton, M.D.
Statistician:	David Cuthbertson, MS
Consortium:	Brittle Bone Disorders
Participating Sites:	Baylor College of Medicine; Shriners Hospital for Children, Montreal; Kennedy Krieger Institute / Hugo W. Moser Research Institute; Hospital for Special Surgery; University of California Los Angeles; Oregon Health and Science University; University of Nebraska Medical Center
Activation Date:	TBD
Sample Size:	16
Target Enrollment Period:	August 2016-August 2019
Study Design:	Interventional
Primary Study Objective:	To evaluate the safety of single and repeat dose administrations of fresolimumab in adult patients with moderate-to-severe OI.
Secondary Study Objective(s):	To determine the effects of fresolimumab on bone remodeling, areal bone mineral density, pain scores, pulmonary function tests and quality of life for patients on fresolimumab therapy.
Study Population and Main Eligibility/ Exclusion Criteria:	**Inclusion criteria (Stage 1 and Stage 2)** 1. Willing and able to provide signed informed consent. 2. Age ≥ 18 years 3. Diagnosis of moderate-to-severe OI based on history of more than 20 fractures in lifetim**e.** 4. Glycine substitution in *COL1A1* or *COL1A2,* or pathogenic variants in *CRTAP*, *PPIB*, or *LEPRE1* (if genetic information is unavailable at screening, this may be assessed at screening visit on a clinical or research basis) 5. Negative urine pregnancy test and ability to use acceptable birth control method for entire duration of the study (if subject is of child-bearing potential) 6. Males who enroll in the study (and their partners) should agree to use an acceptable form of birth control for the entire duration of the study **Exclusion criteria (Stage 1 and Stage 2)** 1. Long bone fracture less than 3 months of screening. These patients can be rescreened after radiologically documented healing of fracture. If individual sustains fracture in the period after the screening visit but before the day 1 of the trial, rescreening will be allowed after 3 months from the date of the fracture 2. Instrumentation in the lumbosacral (LS) and both hips that prevents reliable bone mineral density (BMD) assessment in at least one site

	3. Known unhealed fracture involving a long bone (Nonunion or malunion of greater than 1 year duration will not be considered as unhealed fracture). 4. Vitamin D < 15 ng/dL; rescreening for vitamin D levels will be allowed after supplementation 5. Serum albumin-corrected calcium levels below 8 mg/dL. Rescreening will be allowed after calcium supplementation. 6. Hemoglobin < 10 g/dL 7. Platelet count < 75,000/$mm^{3;}$ rescreening will be allowed to confirm that this is not due to a technical error 8. Prothrombin time/ (PT/INR) international normalized ratio > 1.5 times Upper Limit of Normal (ULN). 9. EKG with QTc of > 450 ms (if QTc is prolonged on one EKG, repeat EKG may be done at the same visit for confirmation, if subsequent EKG shows QTc < 450 ms, subject will be eligible for enrollment) 10. Clinical or laboratory abnormality of Grade III or higher as assessed by CTCAE v4.0 which in the view of investigator would compromise safety 11. History of known allergy or hypersensitivity to fresolimumab 12. Current clinically significant infection. Rescreening will be allowed after resolution of infection. 13. Personal history of basal cell carcinoma, squamous cell carcinoma or keratoacanthomas 14. Any personal history of cancer, recent or remote 15. Any personal history of precancerous condition or lesions including actinic keratosis, atypical moles, Barret's esophagus, or cervical intraepithelial cancer. 16. Evidence of untreated cavities or planned invasive dental work during the study period. 17. Any history of organ transplantation. 18. Any known or suspected valvular heart disease. (Valvular heart disease will be defined by these criteria: 1) history of hemodynamically significant known valvular stenosis or regurgitation; OR 2) presence of grade 3 or higher cardiac murmur at screening visit; OR 3) any history of valvular replacement; OR 4) echocardiographic evidence of any clinically significant valvular stenosis or regurgitation). Trace or trivial valvular regurgitation will not be considered as an exclusion criterion. 19. Anticipated skeletal surgery in the study period. 20. Osteotomy less than 5 months of screening. 21. Prior treatment with zoledronic acid or pamidronate less than 12 months of screening OR oral bisphosphonates less than 6 months of screening OR teriparatide less than one year of screening. 22. Active treatment with systemic glucocorticoids (equivalent of greater than 5 mg of prednisone per day for more than 2 weeks) 3 weeks before screening visit or anticipated treatment of greater than 2 week duration during the study period. 23. Current and daily treatment with antiplatelet agents (aspirin, clopidogrel, dipyridamole, cilostazol, or ticlopidine) 24. Current treatment with anticoagulant medications (low molecular weight heparin analogues, warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban) 25. Documented history of autoimmune disease or immune deficiency. Hashimoto's thyroiditis will not be considered as an exclusion. 26. Evidence of latent tuberculosis by a positive purified protein derivative (PPD) test or Interferon-gamma release assay. 27. Currently receiving another investigational agent in a research study, or less than 30 days since ending treatment on another

	investigational drug study. 28. Current or planned pregnancy at any time during the study period. 29. Nursing mothers. 30. In the opinion of the investigator, inability to fully comply with the study requirements or participation in the study exposes the subject to undue risk.

Treatment	
Agent:	GZ402669 or fresolimumab or GC1008, Human Anti-Transforming Growth Factor-β 1, 2, 3 Monoclonal Antibody
Dosage, schedule, route of administration:	**Single dose study (Stage 1):** **Group 1** • 4 subjects will receive a single intravenous infusion of fresolimumab at a dose of 1 mg/kg body weight. Maximal body weight used for calculation of the drug dose is 80 kg; for those weighing greater than 80 kg, the drug dose will be calculated using a weight of 80 kg. Total duration of study participation per subject is 6 months. **Group 2** • 4 subjects will receive a single intravenous infusion of fresolimumab at a dose of 4 mg/kg body weight. Maximal body weight for calculation of the drug dose is 80 kg; for those weighing greater than 80 kg, the drug dose will be calculated using a weight of 80 kg. Total duration of study participation per subject is 6 months. **Repeat dose study (Stage 2):** **Group 1** • 4 subjects receive four intravenous infusions of fresolimumab at months 0, 3, 6, and 9, with a follow up period of 3 months. Total duration of study participation 12 months. **Group 2** • 4 subjects receive two intravenous infusions of fresolimumab at months 0 and 6, with a follow up period of 6 months. Total duration of study participation is 12 months.
Safety Issues:	Fresolimumab has been investigated in humans. The investigators brochure provides additional safety information. This will be provided to investigators as supplemental material to the protocol.
Primary Outcome Measures:	**Single dose study (Stage 1):** 1) Pharmacokinetics of fresolimumab with single dose administration 2) To evaluate the safety of single administration of fresolimumab in adults with moderate-to-severe OI with respect to: • Vital signs • Laboratory variables • EKG (Corrected QT interval) • Adverse events and serious adverse events **Repeat dose study (Stage 2):** To evaluate the safety of repeat dose administrations of fresolimumab in adults with moderate-to-severe OI with respect to: • Vital signs • Laboratory variables • EKG • Adverse events and serious adverse events

Secondary Outcome Measures:	**Single dose study (Stage 1):** Effect of fresolimumab with respect to: ● Markers of bone turnover in blood (type 1 procollagen, N-terminal or P1NP, Osteocalcin or Ocn, and C-terminal telopeptide or CTX) ● Areal bone mineral density (aBMD) at the hip or the lumbar spine as measured by dual-energy X-ray absorptiometry (DXA) scan **Repeat dose study (Stage 2):** Effect of fresolimumab with respect to: ● Markers of bone turnover in blood (type 1 procollagen, N-terminal or P1NP, Osteocalcin or Ocn, and C-terminal telopeptide or CTX) ● Areal bone mineral density (aBMD) at the hip or the lumbar spine as measured by dual-energy X-ray absorptiometry (DXA) scan ● Bone density and estimated strength by pQCT of forearm ● Pain score as assessed by Numeric Rating Scale (NRS) ● Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) as measured by pulmonary function tests ● QOL as assessed by PROMIS® ● Functional capacity as assessed by the 6-minute walk test.
Statistical Considerations (sample size and analysis plan):	This study is designed to assess the safety and tolerability of fresolimumab in patients with Osteogenesis Imperfecta. **Sample Size:** No formal sample size calculations will be done for this study. The sample size was selected to allow for an initial assessment of safety in this population, dose range and feasibility of enrollment in this rare disorder. The sample size is 8 for the single dose study and 8 for the repeat dose study. Participants enrolled in Stage 1 of this study may be enrolled in Stage 2 of the study if they meet eligibility. The overall enrollment will be 16. If needed, 2 additional patients will be enrolled in the repeat dose study to account for a dropout rate of 20%. Treatment-Related Adverse Events will be summarized by dose groups. Changes in Vital signs (heart rate, blood pressure, respiratory rate, and body temperature), EKG, changes in laboratory assessments and physical examination findings, and patient-reported symptoms will be described. These variables will assess the primary endpoint of safety. Percent change in bone remodeling markers will be analyzed using a mixed model. BMD in the lumbar spine and the hip at 6 months for the single dose study and at 12 months for the multiple dose study will be compared to pretreatment levels using a Wilcoxon Signed Rank test. Percent change in the variables of the pulmonary function tests, and changes in the 6-minute walk test and the Numeric Rating Scale (NRS) for pain will be evaluated by Wilcoxon Signed Rank test. Values for derived pharmacokinetic variables, including Cmax, area under the curve, distribution, half-life (T1/2a), elimination half-life (T1/2b), clearance (CL), and volume of distribution at steady state (Vss), will be calculated as previously described and summarized by dose-group using descriptive statistics.
Sponsors (federal, state, foundation and industry support):	National Institutes of Health (NIH), The Osteogenesis Imperfecta Foundation (OIF), Genzyme

1.1 Overview

Osteogenesis imperfecta (OI) refers to a group of heritable disorders of connective tissue. Individuals with OI present with predominant involvement of the bone that includes low bone mass, increased bone fragility, recurrent fractures, and bone deformities. In addition, extraskeletal symptoms like cardiac valvular insufficiency,

ligamentous laxity, and lung abnormalities add to the significant morbidity of the disorder. The current medical therapy for OI is limited to medications that are FDA-approved for treatment of osteoporosis. Bisphosphonates (BPNs), a class of antiresorptive medications, are generally considered as standard of care. Bisphosphonates increase bone mineral density in children and adults with OI. Evidence for reduction of fractures is conflicting and is particularly problematic in adult patients. An alternative approach to increase bone density and bone quality is the use of bone anabolic agents. A recent trial with teriparatide, a bone anabolic agent approved for treatment of osteoporosis, showed that efficacy of such therapy is rather limited in those who need therapy the most, i.e., individuals with moderate-to-severe OI.

Transforming growth factor beta (TGFβ) is a cytokine that belongs to a superfamily of ligands. Members of the TGFβ family maintain homeostasis in many organ systems. In bone, TGFβ acts as a central coordinator of bone remodeling. Recently, it was discovered that increased TGFβ activity in the bone matrix is a primary mechanism contributing to the decreased bone mass, impaired biomechanical properties, and susceptibility to fracture in OI. These data suggest that inhibition of TGFβ could be a potential disease-specific therapy in OI.

This is a multi-center interventional study to determine the safety of fresolimumab therapy in individuals with moderate-to-severe OI. It will be conducted by the Brittle Bone Disorders Consortium, which is part of the Rare Disease Clinical Research Network (RDCRN) and comprises of multiple distinct Rare Disease Clinical Research Consortia (RDCRC) and one Data Management & Coordinating Center (DMCC). The National Institutes of Health (NIH) and its Office of Rare Diseases Research (ORDR), the National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute of Dental and Craniofacial Research (NIDCR) and the National Institute of Child Health and Human Development (NICHD) provide oversight for the Brittle Bone Disease Clinical Research Consortium.

We propose to:

1) Evaluate the safety of a single dose injection of fresolimumab in adult patients with OI (Stage 1).

2) Evaluate the safety of repeated dose administration of fresolimumab in adult patients with OI (Stage 2).

2. Specific Aims (Hypothesis and Objectives)

We propose to conduct a Phase 1 clinical trial of fresolimumab (a human pan-TGFβ-neutralizing monoclonal antibody) in patients with moderate-to-severe OI by accomplishing the following specific aims:

Aim 1. Evaluate the safety of a single administration of fresolimumab in adult patients with OI (Stage 1). We will perform a multicenter, dose-ranging, study in adults with moderate-to-severe OI. Subjects will be assigned to receive a single-dose of either 1 mg/kg (group 1) or 4 mg/kg (group 2) of fresolimumab (n=4 per group). The primary endpoints will be safety measures that will be assessed over a period of 6 months. The secondary endpoints will be changes in markers of bone remodeling and bone mineral density as compared to pretreatment values.

Aim 2. Evaluate the safety of repeated dose administration of fresolimumab in adult patients with moderate-to-severe OI (Stage 2). This will also be a multicenter wherein fresolimumab will be administered every three months (group 1) or every six months (group 2) for a total treatment period of 12 months (n=4 patients per group). The dose to be administered (1 or 4 mg/kg) will be chosen after completion of Stage 1. The primary Stage 2 endpoint will be safety measures assessed over 12 months. The secondary endpoints will be changes in markers of bone remodeling, bone mineral density, estimated strength as assessed by peripheral QCT of the forearm, pulmonary function tests, pain as assessed by NRS, QOL as assessed by the PROMIS questionnaire, and changes in the 6-minute walk test.

3. Background

3.1 Disease Description

Osteogenesis imperfecta (OI) refers to a group of heritable disorders of connective tissue. Individuals with OI present with predominant involvement of bone that includes low bone mass, increased bone fragility, recurrent fractures, and bone deformities. In addition, extraskeletal manifestations like cardiac valvular insufficiency, ligamentous laxity, and lung abnormalities add to the significant morbidity of the disorder. [1] Intrauterine fractures and perinatal mortality are typical in the severe forms of the disease. A prevalence of 1 in 15,000–20,000 births and an estimated patient population of ~ 25,000 in the United States make OI a prototype rare disease. [1,2] The majority of patients with OI have mutations in either COL1A1 or COL1A2, which encode components of type I collagen, the major matrix protein in bone. More recently, mutations in genes involved in post-translational modification of type I collagen, chaperone proteins, signaling molecules, and others have been discovered to cause OI as well. [3-9]

3.2 Current Therapies Available

The current medical therapy for OI is limited to medications that are FDA-approved for treatment of osteoporosis. Bisphosphonates (BPNs), a class of antiresorptive medications, are generally considered as standard of care. The rationale for BPN therapy in OI is that this could increase the bone mineral density, and the increased bone mass albeit with abnormal matrix could potentially reduce fracture rates. Bisphosphonates increase bone mineral density in children and adults with OI; however, their efficacy in reducing fractures is still unclear, particularly in adult patients. [10,11] More recently, human and murine studies have raised concerns that long-term use of BPNs in OI could result in impaired bone quality and adverse effects such as atypical fractures. [12-14] An alternative approach to increase bone density and bone quality is the use of bone anabolic agents. A recent trial with teriparatide, a

bone anabolic agent approved for treatment of osteoporosis, showed that efficacy of such therapy is rather limited in those who need therapy the most, i.e., individuals with moderate-to-severe OI. [15]Thus, the current strategy of repurposing approved anti-osteoporotic medications for OI has significant limitations as these do not target the primary pathogenetic mechanisms involved in the causation of bone fragility. Additionally, none of the current therapies are geared towards treatment of extraskeletal manifestations such as pulmonary disease. Currently, there are no disease-specific therapies for OI, and availability of such modalities would be of significant importance to patients.

3.3 TGF-β is a potential therapeutic target in OI

Transforming growth factor beta (TGFβ) is a cytokine that belongs to a superfamily of ligands including bone morphogenetic proteins and activins. Members of the TGFβ family maintain homeostasis in many organ systems. In bone, TGFβ acts as a central coordinator of bone remodeling by coupling the activity of bone-resorbing osteoclasts and bone-forming osteoblasts.[16] Recently, it was discovered that increased TGFβ activity in the bone matrix is a primary mechanism contributing to the decreased bone mass, impaired biomechanical properties, and susceptibility to fracture in OI. [17] This increased TGFβ signaling was also observed in extraskeletal tissue like the lungs further underscoring the central role of TGFβ dysregulation in OI. In mouse models of moderate-to-severe OI that recapitulate human disease, inhibiting TGFβ with anti-TGFβ antibody (1D11, a murine analog of fresolimumab, Genzyme, USA) resulted in increased bone mass, quality, and strength. [17] Additionally, this approach also rescued the pulmonary abnormalities. These data suggest that inhibition of TGFβ could be a potential disease-specific therapy in OI.

3.4 Fresolimumab, a pan TGFβ neutralizing antibody

Fresolimumab (Genzyme, USA) is an engineered human IgG4 kappa monoclonal antibody capable of neutralizing all mammalian isoforms of TGFβ (i.e., β1, 2, and 3).

3.5 Fresolimumab for inhibition of TGFβ in humans

The safety of fresolimumab has been evaluated by Genzyme in non-clinical studies using rodent and non-human primate models. Fresolimumab has also been used in humans with idiopathic pulmonary fibrosis, idiopathic focal segmental glomeruolosclerosis [18], advanced renal cell carcinoma and malignant melanoma [19] in Genzyme-sponsored clinical studies. The nonclinical and clinical data gathered to date support single- and repeat-dose administration of fresolimumab in humans.

The effects of fresolimumab on bone turnover and bone mass have not been studied, and the sponsor wishes to conduct a phase I study of fresolimumab in a Mendelian skeletal condition with proven over-activity of TGFβ. This would be the first disease-specific therapy to be investigated in humans with OI.

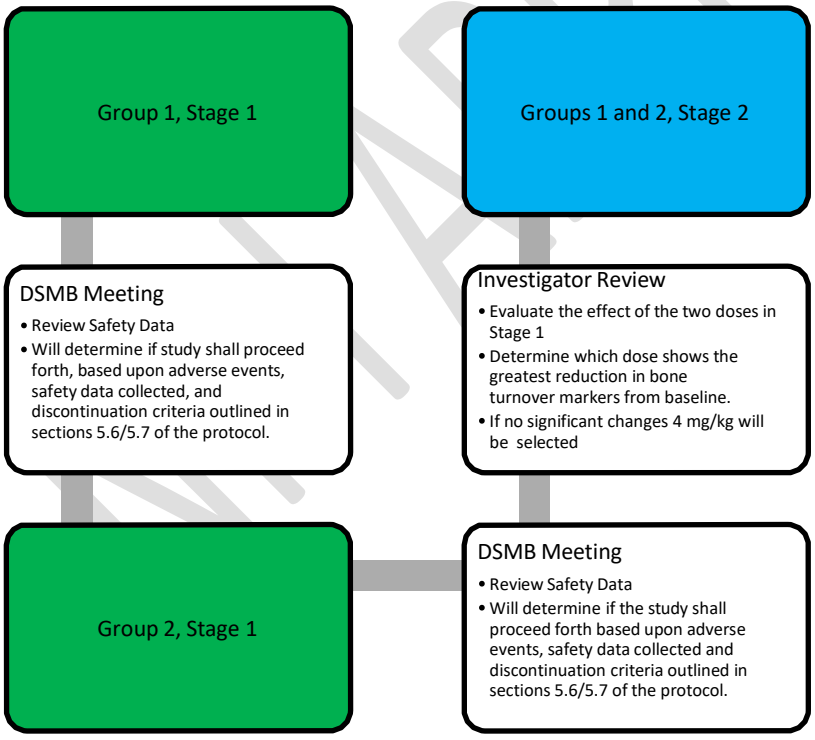
4. Study Design and Methods

This is a multicenter, phase I study to evaluate the safety of single and repeat dose administration of fresolimumab in adult patients with moderate-to-severe OI. Stage I will involve a single dose of fresolimumab wherein those in group 1 will be administered a dose of 1 mg/kg body weight and those in group 2 will be administered a dose of 4 mg/kg body weight; there will be no randomization in this stage. Stage 2 will involve repeat doses of fresolimumab; in this stage, the Data Management Coordinating Center will randomize patients into two groups – individuals in group 1 will receive 4 doses of fresolimumab at months 0, 3, 6, and 9 and individuals in group 2 will receive two doses of fresolimumab at months 0 and 6.

Design

After the four individuals complete the 1 mg/kg dose (group 1, stage 1), an independent Data Safety and Monitoring Board appointed by the National Institute of Health will review the safety data. The decision to proceed with the 4 mg/kg single dose administration (group 2, stage 1) will be determined by the DSMB based on adverse events, safety data collected, and discontinuation criteria outlined in sections 5.6 and 5.7 of the protocol.

If the study proceeds, the study procedures for the 4 mg/kg (group 2, stage 1) will be identical to those for the 1 mg/kg (group 1, stage 1). After completion of the single dose infusion of 4 mg/kg (group 2, stage 1), the DSMB will assess the safety profile of the dose and provide a decision regarding the repeat dose studies (Stage 2).



The Investigators will evaluate the effect of the two doses of fresolimumab in Stage 1 on markers of bone turnover and determine the dose that shows the greatest reduction in bone turnover markers compared to baseline. This dose will be chosen for the repeat dose studies. If there were no significant changes between the bone turnover markers with either dose, the 4 mg/kg dose will be chosen for the repeat dose study.

Study Sites

The study will be conducted at select clinical sites of the Brittle Bone Disorders Consortium (BBD) (https://www.rarediseasesnetwork.org/cms/bbd/). The BBD is a part of the National Center for Advancing Translational Sciences (NCATS) Rare Disease Clinical Research Network (RDCRN). The study procedures are funded through collaboration between the Office of Rare Diseases Research (ORDR), NCATS, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Dental and Craniofacial Research (NIDCR). The Principal Investigators at each site that will conduct the study have significant expertise in the management of OI.

4.1 Inclusion Criteria (Stage 1 and Stage 2)

1. Willing and able to provide signed informed consent.
2. Age ≥ 18 years
3. Diagnosis of moderate-to-severe OI based on history of more than 20 fractures in lifetime.
4. Glycine substitution in *COL1A1* or *COL1A2,* or pathogenic variants in *CRTAP*, *PPIB*, or *LEPRE1* (if genetic information is unavailable at screening, this may be assessed at screening visit on a clinical or research basis).
5. Females of child-bearing potential must have a negative urine pregnancy test, agree to and have the ability to use acceptable birth control method for entire duration of the study.
6. Males who enroll in the study and their partners must agree to use an acceptable form of birth control for the entire duration of the study.

4.2 Exclusion criteria (Stage 1 and Stage 2)

1. Long bone fracture less than 3 months of screening. These patients can be rescreened after radiologically documented healing of fracture. If an individual sustains a fracture in the period after the screening visit but before the day 1 of the trial, rescreening will be allowed after 3 months from the date of the fracture.
2. Instrumentation in the lumbosacral (LS) and both hips that prevents reliable bone mineral density (BMD) assessment in at least one site.
3. Known unhealed fracture involving a long bone (Nonunion or malunion of greater than 1 year duration will not be considered as unhealed fracture).
4. Vitamin D < 15 ng/dL; rescreening for vitamin D levels will be allowed after supplementation.
5. Serum albumin-corrected calcium levels below 8 mg/dL. Rescreening will be allowed after calcium supplementation.
6. Hemoglobin < 10 g/dL.
7. Platelet count < 75,000mm$^{3;}$ rescreening will be allowed to confirm that this is not due to a technical error.
8. Prothrombin time/(PT/INR) international normalized ratio > 1.5 times Upper Limit of Normal (ULN).
9. EKG with QTc of > 450 ms (if QTc is prolonged on one EKG, repeat EKG may be done at the same visit for confirmation, if subsequent EKG shows QTc < 450 ms, subject will be eligible for enrollment.)
10. Clinical or laboratory abnormality of Grade III or higher as assessed by CTCAE v4.0 which in the view of investigator would compromise safety.
11. History of known allergy or hypersensitivity to fresolimumab.

12. Current clinically significant infection. Rescreening will be allowed after resolution of infection.
13. Personal history of basal cell carcinoma, squamous cell carcinoma or keratoacanthomas.
14. Any personal history of cancer, recent or remote.
15. Any personal history of precancerous condition or lesions including actinic keratosis, atypical moles, Barret's esophagus, or cervical intraepithelial cancer.
16. Evidence of untreated cavities or planned invasive dental work during the study period.
17. Any history of organ transplantation.
18. Any known or suspected valvular heart disease. (Valvular heart disease will be defined by these criteria: 1) history of hemodynamically significant known valvular stenosis or regurgitation; OR 2) presence of grade 3 or higher cardiac murmur at screening visit; OR 3) any history of valvular replacement; OR 4) echocardiographic evidence of any clinically significant valvular stenosis or regurgitation). Trace or trivial valvular regurgitation will not be considered as an exclusion criterion.
19. Anticipated skeletal surgery in the study period.
20. Osteotomy less than 5 months of screening.
21. Prior treatment with zoledronic acid or pamidronate less than 12 months of screening OR oral bisphosphonates less than 6 months of screening OR teriparatide less than one year of screening.
22. Active treatment with systemic glucocorticoids (equivalent of greater than 5 mg of prednisone per day for more than 2 weeks) 3 weeks before screening visit or anticipated treatment of greater than 2 week duration during the study period.
23. Current and daily treatment with antiplatelet agents (aspirin, clopidogrel, dipyridamole, cilostazol, or ticlopidine)
24. Current treatment with anticoagulant medications (low molecular weight heparin analogues, warfarin, dabigatran, rivaroxaban, apixaban, or edoxaban)
25. Documented history of autoimmune disease or immune deficiency. Hashimoto's thyroiditis will not be considered as an exclusion.
26. Evidence of latent tuberculosis by a positive purified protein derivative (PPD) test or Interferon-gamma release assay.
27. Currently receiving another investigational agent in a research study, or less than 30 days since ending treatment on another investigational drug study.
28. Current or planned pregnancy at any time during the study period.
29. Nursing mothers.
30. In the opinion of the investigator, inability to fully comply with the study requirements or participation in the study exposes the subject to undue risk.

Women

If the subject is a female, she will be asked about her menstrual cycle history (including date of last period; menses regularity; typical duration and normalcy; any abnormal discharges; and excessive bleeding). If she is of childbearing potential and is sexually active, she must be non-lactating and have a negative urine pregnancy test at Screening and Baseline/Day1. The subject must agree to use one of these acceptable methods of contraception until study termination:

a) Hormonal contraceptive: birth control pills, injection, patch, vaginal ring or implant
b) Condom or diaphragm, with spermicide
c) Intrauterine device (IUD)

d) Sterile male partner (vasectomy performed at least 6 months prior to the study) Absolute abstinence from all sexual activity is also acceptable.

Men

If the subject is a man who has not had a vasectomy, he and his female partner must agree to practice appropriate contraception, as described above, during the study.

4.3 Rescreening

Rescreening will be allowed in patients initially excluded for these criteria:

1. Fracture less than 3 months of screening. These patients can be rescreened after radiologically documented healing of fracture. If individual sustains fracture in the period after the screening visit but before the day 1 of the trial, rescreening will be allowed after 3 months from the date of the fracture.
2. Vitamin D < 15 ng/dL; rescreening for vitamin D levels will be allowed after supplementation.
3. Serum albumin-corrected calcium levels below 8 mg/dL; rescreening will be allowed after calcium supplementation.
4. Current clinically significant infection; rescreening will be allowed after resolution of infection.
5. Platelet count less than 75,000/mm^3. Rescreening with a second CBC will be allowed.

4.4 Recruitment of Participants

Recruitment will occur through the clinical practices of each site investigator, through the RDCRN Contact Registry, and, as needed, via mailings to appropriate clinicians in the investigators' catchment areas and to the patient members of the Osteogenesis Imperfecta Foundation.

Recruitment will occur by physicians, study nurses, and research coordinators. Details of the goals of the research and the risk and benefits of the protocol will be reviewed with each potential study participant. Strict patient confidentiality will be observed throughout all aspects of the study. Potential subjects may be requested to provide medical records prior to consenting to the study to establish eligibility. In this case a medical records release form will be completed to request clinical lab results such as genetic confirmation data and historical X-rays. While medical records will be reviewed by members of the research team, no individually identifiable patient data will be distributed to non-research or care-giving team members.

4.5 Retention Strategies

OI is a rare disorder that is managed by a small number of specialists. Most of these specialists work regularly with the OIF, participate in scientific and clinical research meetings and have the expertise to provide medical and surgical care to individuals with OI. These clinical relationships provide an avenue for increased communication that can facilitate retention. Furthermore, this study may provide benefit to the participants that would enhance retention. Nurses/genetic counselors/clinical research coordinators at each site will work to maintain close contact with participants, including regular clinic visits, newsletters and communication by phone, email and web sites. Study related testing for this research protocol will be performed at no charge to the participant. Finally, we will reimburse families for some travel related costs.

4.6 Investigational Product(s)

Fresolimumab will be supplied as a sterile lyophilized powder for reconstitution. The sterile lyophilized powder is intended to be reconstituted with 5.1 mL (50 mg vial) sterile Water for Injection (sWFI). For the vials containing fresolimumab this will result in a protein concentration of approximately 10 mg/mL in a 50 mM sodium phosphate buffer at pH 7.1, containing 25 mM sodium chloride, 3% mannitol, 1% sucrose, and 0.01% Polysorbate-80.

Packaging

Packaging and distribution services will be coordinated by the Sponsor or its designee for all study sites. Fresolimumab is stored in clear glass vials of 5 mL capacity (nominal), which meet the USP standard for Type I glass, closed by a siliconized butyl rubber stopper. Each vial contains approximately 50 mg of IP. All label text will comply with country specific regulatory requirements.

Storage

Upon receipt by the clinical site, IP must be stored at 2 to 8°C (35.6 to 46.4 °F), in a limited-access area until preparation for infusion. Reconstituted fresolimumab is stable for up to 24 hours after reconstitution with sWFI at either room temperature or under refrigeration (between 2 to 8° C or 35.6 to 46.4° F). Although stable for up to 24 hours under these conditions, fresolimumab in sWFI should be used immediately. All used and unused vials should be stored and organized in a secure area for later drug accountability.

4.7 Single Dose Administration Study (Stage 1)

Primary objective

1. Pharmacokinetics of fresolimumab with a single dose administration
2. To evaluate the safety of a single dose administration of fresolimumab in adults with moderate-to-severe OI with respect to:
    - Vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
    - Laboratory variables.
    - EKG (Corrected QT interval).
    - Adverse events and serious adverse events.

Secondary Objectives

Effect of fresolimumab with respect to:

- Markers of bone turnover in blood (type 1 procollagen, N-terminal or P1NP, Osteocalcin or Ocn, and C-terminal telopeptide or CTX).
- Areal bone mineral density (aBMD) at the hip or the lumbar spine as measured by dual-energy X-ray absorptiometry (DXA) scan.

Dose

- 4 subjects will receive a single intravenous infusion of fresolimumab at a dose of 1 mg/kg body weight. Maximal body weight used for calculation of the drug dose

is 80 kg; for those weighing greater than 80 kg, the drug dose will be calculated using a weight of 80 kg. Total duration of study participation per subject is 6 months.

- 4 subjects will receive a single intravenous infusion of fresolimumab at a dose of 4 mg/kg body weight. Maximal body weight for calculation of the drug dose is 80 kg; for those weighing greater than 80 kg, the drug dose will be calculated using a weight of 80 kg. Total duration of study participation per subject is 6 months.

The two doses have been selected based on safety data from previous studies conducted with fresolimumab that have shown that single doses up to 4 mg/kg have been well tolerated.

Study Procedures

This study will require six visits at a participating clinical site of the BBD consortium. Laboratory tests, ECGs, and radiographs obtained during this study will be interpreted locally by the PIs.

A patient can be enrolled in the study only after an in-person screening visit which will be conducted at BCM. Day 1 visit, during which the participant will receive the study medication will have to be an in-person visit at BCM. Participants are expected to come in for the follow up visits to the study site at BCM. However if there are unforeseen circumstances, or safety reasons (e.g., COVID-19) due to which a participant is unable to travel to BCM, for the follow up visits, an attempt will be made to accommodate study procedures virtually and/or at a remote site which is close to the place of the residence.

Screening visit procedures

- Obtain informed consent.
- Record medical history.
- Determine if participant has used or is using an exclusionary medication.
- Determine if participant plans to have invasive dental work or skeletal surgery during the period of the study.
- Perform physical examination.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Measure height and weight.
- Collect blood sample for laboratory tests (Safety: comprehensive metabolic panel (CMP), complete blood count (CBC), PT/INR, vitamin D testing, bone remodeling markers [serum C-terminal telopeptide of type 1 collagen (CTX), Osteocalcin (Ocn), and amino-terminal propeptide of type I collagen (P1NP)], and lymphoblast culture).
- Confirm that the subject has a genetic test demonstrating that s/he has a Glycine substitution in *COL1A1* or *COL1A2,* or pathogenic variants in *CRTAP*, *PPIB*, or *LEPRE1.* If not present, collect sample for DNA testing.
- Collect urine sample for laboratory test (Safety: urinalysis OR urine dipstick, urine pregnancy test for women of child- bearing age).
- Perform skeletal survey (if historical x-rays are not available to review and ascertain the bony deformities or scoliosis).
- Perform a 12-lead EKG.

- Perform tuberculosis screening by a positive purified protein derivative (PPD) test or Interferon-gamma release assay.

Prior to enrollment (Day 1) screening eligibility criteria for each subject will be reviewed by participating investigators. Individuals who meet the criteria for enrollment will have Study Visit 1 within 60 days of screening.

Day 1 visit procedures (Baseline)

- Review and confirm that the subject meets all criteria for inclusion.
- Confirm that the subject would not be excluded based on screening laboratory tests, a clinically significant infection, a recent fracture or use of any medications since the screening visit that would exclude them from participation.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Collect urine from female subjects to determine pregnancy status.
- Perform DXA scan of the lumbar spine (test may not be performed if there is significant scoliosis or the patient has had spinal instrumentation).
- Perform DXA scan total hip and femoral neck (test may not be performed if there are pins or rods in the region of interest).
- Collect blood for pharmacokinetics prior to infusion of fresolimumab
- Intravenous Infusion of fresolimumab over 30 minutes.
- Collect blood for pharmacokinetics after the end of the infusion.
- Subjects will be monitored for three hours for any infusion-related reactions (document adverse events) and will be discharged home.

Day 15 visit procedures

- Perform a physical exam.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Record adverse events assessment including history of any oral or mucosal bleeding.
- Perform a 12-lead EKG.
- Collect blood for laboratory tests (Safety: CBC, CMP, PT/INR; Pharmacokinetics; Lymphoblast culture).
- Collect urine sample for laboratory test (Safety: urinalysis OR urine dipstick).
- Document adverse events.

Day 30 visit procedures

- Perform a physical exam.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Collect blood for laboratory tests (Safety: CBC, CMP, PT/INR; Pharmacokinetics; Bone remodeling markers).
- Collect urine sample for laboratory test (Safety: urinalysis OR urine dipstick).
- Record adverse events assessment including history of any oral or

mucosal bleeding.

Day 90 visit procedures

- Perform a physical exam.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Record medical history.
- Collect blood for laboratory tests (Safety: CBC, CMP, PT/INR; Pharmacokinetics; Bone remodeling markers).
- Collect urine sample for laboratory test (Safety: urinalysis OR urine dipstick).
- Document adverse events.

Day 180 visit procedures

- Perform a physical exam.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Record adverse events.
- Collect blood for laboratory tests (Safety: CBC, CMP, PT/INR; Pharmacokinetics; Bone remodeling markers).
- Collect urine sample for laboratory test (Safety: urinalysis OR urine dipstick)
- Perform a 12-lead EKG.
- Perform DXA scan of the lumbar spine (test may not be performed if there is significant scoliosis or the patient has had spinal instrumentation).
- Perform DXA scan total hip and femoral neck (test may not be performed if there are pins or rods in the region of interest).
- Document adverse events.

4.8 Repeat Dose Administration study (Stage 2)

Primary objective

To evaluate the safety of repeat dose administrations of fresolimumab in adults with moderate-to-severe OI with respect to:

- Vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Laboratory variables.
- EKG.
- Adverse events and serious adverse events.

Secondary Objectives

Effect of fresolimumab with respect to:

- Markers of bone turnover in blood (type 1 procollagen, N-terminal or P1NP, Osteocalcin or Ocn, and C-terminal telopeptide or CTX).
- Areal bone mineral density (aBMD) at the hip or the lumbar spine as measured by dual-energy X-ray absorptiometry (DXA) scan.
- Bone density and estimated strength by pQCT of forearm.
- Pain score as assessed by Numeric Rating Scale (NRS).

- Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) as measured by pulmonary function tests
- QOL as assessed by PROMIS®.
- Functional capacity as assessed by the 6-minute walk test.

Dose
Group 1

- 4 subjects receive four intravenous infusions of fresolimumab- months 0, 3, 6, and 9, with a follow up period of 3 months (total duration of study participation 12 months).

Group 2

- 4 subjects receive two intravenous infusions of fresolimumab- months 0 and 6, with a follow up period of 6 months (total duration of study participation 12 months).

The dose regimen has been selected based on the duration of bone remodeling cycle that can vary from 3-6 months. The dose regimen and duration are similar to studies that have been conducted with denosumab (Prolia ®), a monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B ligand (RANKL), which has been approved for the treatment of osteoporosis. [24] Repeat doses of both 1 mg/kg and 4 mg/kg body weight of fresolimumab, have been studied in a trial titled "A Phase 2, Multicenter, Double-Blind, Parallel Dosing, Randomized Study of Fresolimumab or Placebo in Patients with Steroid-Resistant Primary Focal Segmental Glomerulosclerosis" under IND 100054. This study had four monthly IV administrations of fresolimumab at either 1 mg/kg or 4 mg/kg or placebo with treatment duration of 12 weeks and observation duration of 24 weeks after last dose of study medication. The dose and the number of doses being proposed for our study are similar but far less frequent than used in the study under IND 100054.

Study Procedures

This study will require up to eight visits at a participating clinical site of the BBD consortium. Laboratory tests, ECGs, and radiographs obtained during this study will be interpreted locally by the PIs.

A patient can be enrolled in the study only after an in-person screening visit which will be conducted at BCM. Day 1 visit, during which the participant will receive the study medication will have to be an in-person visit at BCM. Participants are expected to come in for the follow up visits to the study site at BCM. However if there are unforeseen circumstances, or safety reasons (e.g., COVID-19) due to which a participant is unable to travel to BCM, for the follow up visits, an attempt will be made to accommodate study procedures virtually and/or at a remote site which is close to the place of the residence.

Screening visit procedures

- Obtain informed consent.
- Record medical history.
- Determine if participant has used or is using an exclusionary medication.
- Determine if participant plans to have invasive dental work or skeletal surgery during the period of the study
- Perform physical examination.

- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Measure height, weight, arm span.
- Collect blood sample for laboratory tests (Safety: comprehensive metabolic panel (CMP), complete blood count (CBC), PT/INR, vitamin D testing, bone remodeling markers [serum C-terminal telopeptide of type 1 collagen (CTX), Osteocalcin (Ocn), and amino-terminal propeptide of type I collagen, P1NP)], and lymphoblast culture for gene expression studies).
- Confirm that the subject has a genetic test demonstrating that s/he has a Glycine substitution in *COL1A1* or *COL1A2,* or pathogenic variants in *CRTAP*, *PPIB*, or *LEPRE1.* If not present, collect sample for DNA testing.
- Collect urine sample for laboratory test (Safety: urinalysis OR urine dipstick, urine pregnancy test for women of child-bearing age).
- Perform skeletal survey (if historical x-rays are not available to review and ascertain the bony deformities or scoliosis).
- Perform a 12-lead EKG.
- Perform tuberculosis screening by a positive purified protein derivative (PPD) test or Interferon-gamma release assay.

Prior to enrollment (Day 1) screening eligibility criteria for each subject will be reviewed by participating investigators. Individuals who meet the criteria for enrollment will have Study Visit 1 within 60 days of screening.

Day 1 visit procedures (Baseline)

- Review and confirm that the subject meets all criteria for inclusion.
- Confirm that the subject would not be excluded based on screening laboratory tests, a clinically significant infection, a recent fracture or use of any medications since the screening visit that would exclude them from participation.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Collect urine from female subjects to determine pregnancy status.
- Perform DXA scan of the lumbar spine (test may not be performed if there is significant scoliosis or the patient has had spinal instrumentation).
- Perform DXA scan total hip and femoral neck (test may not be performed if there are pins or rods in the region of interest).
- Perform a peripheral quantitative CT (pQCT) of the forearm.
- Perform a pulmonary function test.
- Perform a 6-minute walk test.
- Collect Numeric Rating Scale (NRS) and PROMIS® 29 questionnaire responses.
- Collect blood for immunogenicity (measure antibodies against fresolimumab) and for pharmacokinetics prior to infusion of fresolimumab.
- Intravenous infusion of fresolimumab over 30 minutes.
- Collect blood for pharmacokinetics after the end of the infusion.
- Subjects will be monitored for three hours for any infusion-related

reactions (document adverse events) and will be discharged home.

Day 15 visit procedures

- Perform a physical exam.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Perform a 12-lead EKG.
- Collect blood for laboratory tests (Pharmacokinetics; Immunogenicity; Lymphoblast culture).
- Document adverse events include bleeding assessment.

Day 30 visit procedures

- Perform a physical exam.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Collect blood for laboratory tests (Safety: CBC, CMP, PT/INR; Pharmacokinetics; Bone remodeling markers; Immunogenicity; Lymphoblast culture).
- Collect urine sample for safety test (urinalysis OR urine dipstick).
- Record adverse events assessment including history of any oral or mucosal bleeding.

Day 90 visit procedures

- Perform a physical exam.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Collect NRS responses.
- Collect blood for laboratory tests (Safety: CBC, CMP, PT/INR; Pharmacokinetics; Bone remodeling markers; Immunogenicity; Lymphoblast culture).
- Collect urine sample for laboratory test (Safety: urinalysis OR urine dipstick, urine pregnancy test for women of child-bearing age).
- Perform a 12-lead EKG.
- The cohort of subjects randomized to receive four infusions of study drug will receive second dose of fresolimumab. The cohort of subjects randomized to receive two infusions of study drug will not receive any drug during this visit.
- Intravenous infusion of fresolimumab over 30 minutes.
- Collect blood for pharmacokinetics after the end of the infusion.
- Document adverse events.

Day 180 visit procedures

- Perform a physical exam.
- Measure vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Collect NRS and PROMIS® 29 responses.
- Collect blood for laboratory tests (Safety: CBC, CMP, PT/INR;

Pharmacokinetics Bone remodeling markers; Immunogenicity)
- Collect urine sample for laboratory test (Safety: urinalysis OR urine dipstick, urine pregnancy test for women of child-bearing age.)
- The cohort of subjects randomized to receive four infusions of study drug will receive the third dose of fresolimumab. The cohort of subjects randomized to receive two infusions of study drug will receive the second.
- Intravenous Infusion of fresolimumab over 30 minutes.
- Collect blood for pharmacokinetics after the end of the infusion.
- Document adverse events

Day 270 visit procedures
- Perform a physical exam.
- Measure Vital signs - heart rate, blood pressure, respiratory rate, and body temperature.
- Collect NRS responses.
- Collect blood for laboratory tests (Pharmacokinetics; Bone remodeling markers).
- Collect urine for urine pregnancy test in women.
- The cohort of subjects randomized to receive four infusions of study drug will receive fourth dose of fresolimumab. The cohort of subjects randomized to receive two infusions of study drug will not receive any drug during this visit.
- Intravenous Infusion of fresolimumab over 30 minutes.
- Collect blood for pharmacokinetics after the end of the infusion.
- Document adverse events.

Day 360 visit procedures
- Perform a physical exam
- Measure Vital signs - heart rate, blood pressure, respiratory rate, and body temperature (including height, weight, arm span)
- Collect NRS and PROMIS® 29 responses
- Collect blood for laboratory tests (Safety: CBC, CMP, PT/INR; Pharmacokinetics; Bone remodeling markers; Immunogenicity; Lymphoblast culture)
- Collect urine sample for laboratory test (Safety: urinalysis OR urine dipstick, urine pregnancy test for women of child-bearing age.)
- Perform a 12-lead EKG
- Perform DXA scan of the lumbar spine (test may not be performed if there is significant scoliosis or the patient has had spinal instrumentation)
- Perform DXA scan total hip and femoral neck (test may not be performed if there are pins or rods in the region of interest)
- Perform a peripheral QCT
- Perform a pulmonary function test
- Perform a 6-minute walk test
- Document adverse events.

- Subjects' participation will conclude when they are discharged home following this visit.

4.9 Data Elements

Once referred for screening, the participant's diagnostic testing will be reviewed to assure that the correct OI classification has been made and eligibility requirements are met based on study inclusion and exclusion criteria. Data will be collected at study visits per **the Schedule of Events for each study group**. We will use a variety of methods to obtain these data. Certain information will be obtained from a historical review of existing charts and laboratory/treatment data. Other data will be obtained from patients or their families through a standard interview, examination or laboratory/functional testing. The investigators who will perform functional assessments and other critical evaluations will be included as investigators on their local institution's IRB application.

Medical History: Medical history will be recorded on a history and physical examination form.

12-lead EKG: EKG at the screening visit then at 2 subsequent study visits for all study participants.

Bone mineral density: A dual-energy x-ray absorptiometry (DXA) at the lumbar spine, total hip and femoral neck will be performed.

X-rays of the spine: Standard posterio-anterior and lateral views will be taken, preferably in the standing position. If this is not possible, these radiographs will be obtained in the sitting position. If participants not able to sit, the X-rays will be taken in the supine position. Taking each of the two views on a single film (skull base to sacrum) is preferred. All radiographic images will be reviewed at the screening visit to determine eligibility. Historical surveys are acceptable if X-rays taken demonstrate the boney abnormalities that are required as inclusion criteria.

Peripheral Quantitative CT of the forearm: A peripheral quantitative CT (pQCT) will be performed at Baseline and exit visits for those subjects participating in the 2nd stage of the study to determine bone mineral density. Measurements will be performed at the non-dominant forearm. In case of recent fracture (< 2 years before) or the presence of metal at this measurement site, the contralateral forearm will be used. Two sites at the forearm will be analyzed, the metaphysis ('4% site') and the diaphysis ('65% site'). Trabecular bone is analyzed at the 4% site, cortical bone is analyzed at the 65% site. The main outcome measures of these analyses are trabecular volumetric bone mineral density (vBMD, 4% site), cortical vBMD (65% site), bone mineral content (both sites) and section modulus (a measure of bone strength, 65% site).

Pulmonary function tests: These will be performed in participants enrolled in the 2nd stage of the study at baseline and exit visits, according to the American Thoracic Society guidelines. Lung volume measurements will be determined by helium dilution. Arm span will be measured to obtain a corrected height and will be used for calculating predicted lung volumes and flow rates. Vital capacity (VC), residual volume (RV), total

lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and FEV1/FVC will be calculated for each participant to determine whether participants suffer from pulmonary compromise due to an underlying tissue disorder, which may go unrecognized without PFT, or if scoliosis is the actual cause for pulmonary compromise. Restrictive lung disease will be defined as a reduction in the VC and a ratio of FEV1/FVC greater than or equal to 80%. Obstructive lung disease will be defined as a reduction in FEV1 and a ratio of FEV1/FVC less than 80%[8].

6 Minute Walk Test: A 6 minute walk test will be performed at the baseline and exit visits for those subjects enrolled in the 2nd stage of the study to determine the subject's mobility.

Numeric Rating Scale: Pain will be evaluated using the Numeric Rating Scale (NRS). This is a self-report assessment scale for patients who are able to use numbers to rate the intensity of their pain.

PROMIS® 29: This tool will be assessed at the screening, day 180 and day 360 study visits for participants enrolled in the 2nd stage of the study.

All study elements are interpreted locally by the respective PIs.
All laboratory testing will be performed using local laboratories and will be interpreted by the respective PIs.

4.10 Schedule of Events

Single Dose Administration (Stage 1)						
Procedures	**Screening**	**Treatment**				
		1	15	30	90	180
	-60 d window		±3 d window		±7 d window	
Informed Consent	X					
Medical History	X					
Physical Examination	X		X	X	X	X
Vital signs - heart rate, blood pressure, respiratory rate, and body temperature	X	X	X	X	X	X
Height	X					
Weight	X					
Blood/Urine for Safety labs (CBC, CMP, PT/INR, Urinalysis OR Urine Dipstick)	X		X	X	X	X
Blood for Bone remodeling markers (P1NP, Osteocalcin, CTX)	X			X	X	X
Blood for Vitamin D testing	X					
Blood for lymphoblast culture	X		X			
Urine Pregnancy test (if applicable)	X	X				X
Blood for Genetic Testing for *COL1A1, COL1A2, CRTAP, P3H1, or PPIB* mutations [a]	X					
Skeletal survey [b]	X					
12 Lead EKG	X		X			X
DXA Lumbar Spine [c]		X				X
DXA total hip and femoral neck [a]		X				X
Infusion of fresolimumab		X				
Pharmacokinetics		X[e]	X	X	X	X
Adverse event documentation		X	X	X	X	X

a Genetic testing will be done only if the genotype is not known

b If skeletal films are available for review to ascertain the bony deformities or scoliosis, this test will not be done

c Test may not be performed if there is significant scoliosis or the patient has had spinal instrumentation

d Test may not be done if there are pins or rods in the region of interest

e For Day 1 of the study, PK samples will be obtained prior to the infusion of fresolimumab and after the end of the infusion.

Repeat Dose Administration (Stage 2)								
	Screening	Treatment						
		1	15	30	90	180	270	360
Procedures	- 60 d window		±3 d window		± 14 d window			
Informed Consent	X							
Medical History	X							
Physical Examination	X		X	X	X	X	X	X
Vital signs - heart rate, blood pressure, respiratory rate, and body temperature	X	X	X	X	X	X	X	X
Height	X							X
Weight	X							X
Arm-span	X							X
Blood/urine for Safety labs (CBC, CMP, PT/INR, Urinalysis OR Urine	X		X	X	X	X		X
Blood for Vitamin D testing	X							
Bone remodeling markers (P1NP, Ocn, CTX)	X			X	X	X	X	X
Blood for PK[#]		X	X	X	X	X	X	X
Blood for lymphoblast culture	X		X	X	X			X
Blood for Antibody/Immunogenicity testing		X	X	X	X	X		X
Blood for Genetic Testing for *COL1A1, COL1A2, CRTAP, P3H1,*	X							
Urine Pregnancy test (if applicable)	X	X			X	X	X	X
Skeletal survey [b]	X							
12-lead EKG	X		X		X			X
Infusion of fresolimumab		X			X[f]	X	X[f]	
DXA Lumbar Spine [c]		X						X
DXA total hip and femoral neck [a]		X						X
Peripheral quantitative CT (pQCT) of the forearm [e]		X						X
NRS		X			X	X	X	X
PROMIS® 29 QOL		X				X		X
Pulmonary function test		X						X
6-minute Walk test		X						X
Adverse event documentation		X	X	X	X	X	X	X
Bleeding Assessment[g]			X	X				

a Genetic testing will be done only if the genotype is not known,

b If skeletal films are available for review to ascertain the bony deformities or scoliosis, this test will not be done
c this test may not be performed if there is significant scoliosis or the patient has had spinal instrumentation

d this test may not be done if there are pins or rods in the region of interest
e Will not be performed if bone deformities preclude assessment

f Will not be performed if subject is randomized into the study group to receive 2 infusions.

g Any patient who experiences clinically significant bleeding will be referred to their primary physicians or hematology specialists for appropriate work up

PK samples will be obtained prior to the infusion of fresolimumab and after the end of the infusion.

NOTE: For documentation of AE and safety, specific information regarding including history of bleeding episodes, physical examination for peripheral edema, hematomas, and gingival hyperplasia, and urinalysis OR a urine dipstick to evaluate for blood will be conducted.

5. Data and Safety Monitoring Plan

The study protocol will be reviewed and approved by the National Institutes of Health (NIH) before submission to individual center IRBs for approval. Participant enrollment may only begin with IRB approved consent forms.

5.1 Study Oversight

The Study Chair has primary oversight responsibility of this clinical trial. The NIH appointed Data Safety Monitoring Board (DSMB) has oversight responsibility of the Data Safety Monitoring Plan (DSMP) for this clinical trial. The DSMB will review accrual, patterns and frequencies of all adverse events, and protocol compliance every 6 months. The DSMB makes recommendations to the NIH regarding the continuation status of the protocol.

Each site's Principal Investigator and their research team (co-Investigators, research nurses, clinical trial coordinators, and data managers) are responsible for identifying adverse events. Aggregate report- detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures – will be available from the DMCC for site review. Adverse events will be reviewed monthly by the research team. A separate report detailing protocol compliance will also be available from the DMCC for site review on a monthly basis. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

5.2 Adverse Event Definitions and Standards

The Rare Diseases Clinical Research Network defines an adverse event as: "…an unfavorable and unintended sign, symptom or disease associated with a participant's participation in a Rare Diseases Clinical Research Network study."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

An unexpected adverse event is defined as any adverse experience, the specificity or severity of which is not consistent with the risks of information described in the protocol.

Expected adverse events are those that are identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study.

All reported adverse events will be classified using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at National Cancer Institute.

5.3 Expected/ Known Risks/ Discomforts/ Adverse Event Associated with Study Intervention and Procedures: Definition of Expected Adverse Events

Study Drug
TGFβ is a cytokine that has an important physiological role in the regulation of cell proliferation and differentiation, extracellular matrix production, angiogenesis, immune regulation and embryonic development. However, sustained overactivity of TGFβ may play a pathophysiological role in disease states such as fibrotic diseases such as FSGS, IPF, and in oncology. Fresolimumab, a human IgG4 antibody which neutralizes TGFβ1, 2, and 3, has potential in the treatment of fibrotic and oncologic diseases. Given the pleiotropic effects of TGFβ, side effects associated with fresolimumab therapy may be observed. The following is a description of potential risks, precautions, and contraindications based on the results of preclinical safety studies and clinical data.

Epithelial Changes Including Keratoacanthoma
Based on the clinical experience to date, the main epithelial adverse reaction to fresolimumab appears to be adverse events involving the skin, most notably keratoacanthoma (KA) and squamous cell carcinoma (SCC). Keratoacanthomalike epithelial lesions developed in 4 patients who received multiple doses of fresolimumab in the Phase 1 oncology study of patients with advanced melanoma or RCC. Skin biopsies were sent for an independent, blinded pathological analysis from these patients. On review, the 2 cases diagnosed at the site as SCC were interpreted as representing KAs, and in one case involving a patient with prior SCC, an atypical squamous-epithelial-proliferation with KA-like features was read as most consistent with SCC. Therefore, subjects with personal history of cancer are excluded from this study.

Acceleration of Neoplasia
Available literature suggests neutralization of TGFβ does not cause de novo malignancies. In advanced cancers, TGFβ neutralization may ameliorate cancer progression; however, in certain settings such as in the presence of premalignant lesions, it is possible that neutralization of TGFβ may contribute to premalignant/malignant transformation.

As noted above, 2 melanoma patients in the oncology trial developed SCC. One of the 2 patients had a history of SCC and the lesions of both patients spontaneously regressed as is consistent with the natural history of KAs. However, the development of KA/SCC has been mechanistically linked to TGFβ signaling in patients with Ferguson-Smith disease. Therefore, the risk of SCC development is likely mechanistically distinct from the theoretical risk of acceleration of neoplasia.

One patient with FSGS experienced a primitive neuroectodermal tumor (PNET) 2 years after a single 1 mg/kg dose of fresolimumab. The patient died approximately one year later from complications of PNET, primarily respiratory failure. The investigator assessed the PNET to be unrelated to fresolimumab. The Data Monitoring Committees (DMCs) of both the oncology and FSGS Phase 1 studies reviewed this case and concluded that the relationship between fresolimumab and PNET was unlikely because the patient received a single dose of fresolimumab 2 years prior to identification of

the tumor and had prior exposure to multiple immunosuppressive medications.

Patients receiving fresolimumab should be carefully monitored for the development of malignancies.

Bleeding and Anemia
Across the clinical studies, the majority of bleeding adverse events reported have been mild, self-limited events of gum bleeding without associated gingival lesions and nose bleeding without discrete nasal lesions. Anemia was not seen with these mild, self-limited events. Patients should be carefully monitored for the development of anemia and bleeding while receiving fresolimumab.

Immune Modulation
In preclinical studies, there did not appear to be any significant immune-mediated toxicity associated with long-term neutralization of TGFβ in normal mice. No evidence of significant immune dysregulation has been seen in clinical studies to date. Three patients with malignant melanoma and 1 patient with FSGS developed non-disseminated herpes zoster. The FSGS patient had a history of herpes zoster. In 1 of the 4 patients, the herpes zoster event was considered by the reporting physician to be related to therapy. It remains to be determined if fresolimumab increases the risk of herpes zoster. Patients should be carefully monitored for the development of herpes zoster. One FSGS patient developed transient vitiligo and 2 oncology patients developed hypopigmentation of skin or hair. In all 3 patients, the events were considered by the reporting physician to be treatment-related. The mechanism by which fresolimumab could be associated with vitiligo/hypopigmentation could potentially be via immune modulation however alternative non-immune mechanisms may play a role.

Reproductive Function
The effects of fresolimumab on male and female reproductive function or fetal growth and development have not been investigated in formal toxicity studies. Maternal TGFβ levels are elevated during normal pregnancy and may have an important role in establishment and preservation of pregnancy. Additionally, TGFβ has a role in embryonic development including organogenesis. Fresolimumab is an antibody and is expected to be able to cross the placenta and enter the fetal circulation during pregnancy. The effects of fresolimumab in this situation are unknown. There is a theoretical risk that inhibiting TGFβ during pregnancy may adversely affect the establishment and preservation of pregnancy or have adverse effects on embryonic or fetal growth and development. Pregnant or lactating women are excluded from clinical studies of fresolimumab. Women who become pregnant or start lactating during the study will be discontinued from study treatment. Sexually active men or sexually active women of childbearing potential (premenopausal and not surgically sterile) must use contraception or abstinence when being treated with fresolimumab.

Overdose
Animal studies have not clearly identified any acute dose related toxic effects. In the event of fresolimumab overdose, the administration should be immediately discontinued and appropriate precautions should be taken.

Contraindications and Warnings
There are no established contraindications to fresolimumab. Patients with significant hypersensitivity to fresolimumab or product components are excluded from clinical studies with fresolimumab. Continued treatment with fresolimumab should be carefully re-evaluated if significant hypersensitivity is observed. Pregnant or lactating women are excluded from clinical studies of fresolimumab. Women who become pregnant or start lactating during the study will be discontinued from study treatment.

Study Procedures
Blood samples will be drawn for safety labs. It is expected that there may be bruising and mild discomfort at the site of needle insertion when phlebotomy is performed. Fainting may even occur.

Participants will be exposed to radiation during dual-energy X-ray absorptiometry scanning and radiographs. The total amount of radiation that the participant will receive in this study is about 1.1 mSv or 110 mrem, and is approximately equivalent to a uniform whole body exposure of 133 days of exposure to natural background radiation. (Ref http://www.doseinfo-radar.com/RADARDoseRiskCalc.html). Though the biological effects of diagnostic radiation on humans have not been studied directly, the potential risk to an individual associated with techniques used for the assessment of bone status is believed to be very small since radiation doses are low. In 2012 the United Nations Scientific Committee on the Effects of Atomic Radiation stated that for typical background radiation levels (1–13 mSv per year), it is not possible to account for any health effects.

Patients may find the pulmonary function testing, function and mobility assessments and hearing tests to be tiring.

Protection from Risk: The study will be conducted in the Clinical and Translational Science Award (CTSA) Centers or research facilities of our respective institutions comprising the BBD Consortium whenever possible. When a CTSA/research facility is not available, study visits will be conducted in the investigator's clinic.

The study implementers will be nursing staff/coordinators of the Centers with a long experience in care of individuals with OI. If any participant should incur any unexpected and untoward event during the testing procedure, the emergency caregivers, would become available on an immediate basis to provide necessary emergent management.

Female participants will have no radiographic procedures while pregnant.

5.4 Adverse Event Reporting Timeline

- Within **24 hours** (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:
  - Is considered life-threatening/disabling or results in death of subject

  -OR-
  - Is Unexpected/Unanticipated
- Investigators must report all other reportable SAEs within **5 working days** (of learning of the event).
- All other (suspected) reportable AEs must be reported to the RDCRN within **20**

working days of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

5.5 RDCRN Adverse Event Monitoring System (AEMS)

The study will utilize the DMCC Adverse Event Monitoring System. Upon entry of a serious adverse event, the DMCC created AEMS will immediately notify the Study Chair, site PIs, the Medical Review Officer, and any additional agencies (if applicable-industry sponsor, CTEP) of any reported adverse events via email.

Serious adverse events: The NIAMS OSMB/DSMB Safety Officer reviews the causality assessment determined by the PI and comment on attribution and recommend any needed action. A back-up notification system is in place so that any delays in review by the NIAMS OSMB/DSMB Safety Officer beyond a specified period of time are forwarded to a secondary reviewer. The DMCC Adverse Event Monitoring System maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious expected adverse events: Except those listed above as immediately reportable, non-serious expected adverse events that are reported to or observed by the investigator or a member of his/her research team will be submitted to the DMCC in a timely fashion (within 20 working days). The events will be presented in tabular form and given to the NIAMS OSMB/DSMB Safety Officer on a biannual basis. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DMCC will post aggregate reports of all reported adverse events for site investigators and IRBs.

5.6 Unanticipated Problem Reporting

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Per the definition, only a subset of adverse events would be characterized as unanticipated problems. There are other types of incidents, experiences, and outcomes

that are not considered adverse events, but are characterized as unanticipated problems (e.g., breach of confidentiality or other incidents involving social or economic harm). Incidents or events that meet the OHRP criteria for unanticipated problems are to be reported to the IRB, per local institutional reporting requirements. Local institutional reporting requirements to IRBs, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

5.7 Study Discontinuation

The NIH, RDCRN DSMB and local IRBs (at their local site) have the authority to stop or suspend this trial at any time. This study may be suspended or closed if:

- Accrual has been met.
- The study objectives have been met.
- The Study Chair / Study Investigators believe it is not safe for the study to continue.
- The RDCRN DSMB suspends or closes the trial.
- The NIH suspends or closes the trial.
- The FDA suspends or closes the trial.
- If 2 or more subjects experience Grade 4 or higher adverse events as defined by the CTCAE or life threatening AEs not covered by the CTCAE of the same preferred term related to the study medication, excluding conditions present at baseline or those directly related to skeletal complications of Osteogenesis Imperfecta.
- If 2 or more subjects develop cancer.

5.8 Subject Discontinuation

An intent to treat approach will be used. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless patient withdraws consent. Every effort will be made to conduct a final study visit with the participant and participants will be followed clinically until, if applicable, all adverse events resolve.

- Withdrawal of consent.
- Withdrawal by the participant.
- Withdrawal by the investigator.
- Intercurrent illness or event that precludes further visits to the study site or ability to evaluate disease (e.g.-mental status change, large pleural effusion).
- Grade 4 or higher adverse events as defined by the CTCAE or life threatening AEs not covered by the CTCAE of the same preferred term related to the study medication, excluding conditions present at baseline or those directly related to skeletal complications of Osteogenesis Imperfecta.
- Clinically significant allergy or hypersensitivity to fresolimumab.
- Pregnancy.
- QTc interval of > 500msec.
- Clinically significant oral or mucosal bleeding with resulting hemoglobin of < 8g/dL.
- Development of keratoacanthoma, squamous cell or basal cell carcinoma.
- Development of any cancer.

5.9 Data Quality and Monitoring Measures

As much as possible data quality is assessed at the data entry point using intelligent on-line data entry via visual basic designed screen forms. Data element constraints, whether independent range or format limitations or 'relative' referential integrity limitations, can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency.

- Data Monitoring: The RDCRN DMCC identifies missing or unclear data and generates a data query to the consortium administrator contact.
- Data Delinquency Tracking: The Data Management and Coordinating Center will monitor data delinquency on an ongoing basis.

5.10 Quality Control: Study Related Procedures

Accurate, consistent and reliable data will be ensured through the use of standard practices and procedures. The DMCC will audit the Investigators' source data against eCRF entries and verify that the data are accurate.

6. Statistical Considerations

This study is designed to assess the safety and tolerability of fresolimumab in patients with Osteogenesis Imperfecta.

Sample Size: No formal sample size calculations were done for this study. The sample size was selected to allow for an initial assessment of safety in this population and dose range and feasibility of enrollment in this rare disorder. The sample size is 8 for the single dose study and 8 for the repeat dose study. The overall enrollment will be 16.

If needed, 2 additional patients will be enrolled in the repeat dose study to account for a drop-out rate of 20%.

Treatment-Related Adverse Events will be summarized by dose groups. Changes in vital signs, EKG, shifts in laboratory assessments and physical examinations, and patient-reported symptoms will be described. These will assess the primary endpoint of safety. Percent change in bone remodeling markers will be analyzed using a mixed model. BMD in the lumbar spine and the hip at 6 months for single dose study and 12 months for the multiple dose study will be compared to pretreatment levels using a Wilcoxon Signed Rank test. Percent change in the variables of the pulmonary function tests, and change in the 6-minute walk tests, and Numeric Rating Scale (NRS) for pain will be evaluated by Wilcoxon Signed Rank test. Values for derived pharmacokinetic variables, including Cmax, area under the curve, distribution, half-life (T1/2a), elimination half-life (T1/2b), clearance (CL), and volume of distribution at steady state (Vss), will be calculated as previously described and summarized by dose-group using descriptive statistics.

7. Data Management

The results from Screening and data collected during the study will be recorded in the

patient's CRF (either paper or electronic CRF). To maintain confidentiality, the patients will be identified only by numbers or initials. All source documents, records, and reports will be retained by the study site in accordance with 21 CFR 312.62(c). All primary data, or copies thereof (e.g., laboratory records, CRFs, data sheets, correspondence, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the study site archives.

All study data will be collected via systems created in collaboration with the RDCRN Data Management and Coordinating Center and will comply with all applicable guidelines regarding patient confidentiality and data integrity. Biological samples collected for safety testing will be shipped to a CLIA certified laboratory for analysis. Biological samples collected for pharmacokinetics and drug efficacy will be shipped to Genzyme/Sanofi for analysis.

7.1 Registration

Registration of participants on this protocol will employ an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical site.

The DMCC will use a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject. When the participant is registered to participate in the study, using the DMCC provided web-based registration system, the system will assign a participant ID number. Thus each participant will have two codes: the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the DMCC. For all data transfers to the DMCC both numbers will be required to uniquely identify the subject. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the numbers should match to properly identify the participant.

7.2 Data Entry

Data collection for this study will be accomplished with online electronic case report forms. Using encrypted communication links, on-line forms will be developed that contain the requisite data fields.

7.3 Laboratory Data Flow

The DMCC will provide the study with a specimen database that allows tracking of the colletion, storage, and transfer of biological specimens, their submission to laboratories for testing, and the incorporation of laboratory results in the study database.

7.4 Study Records Retention

Patient files and other source data shall be kept for the maximum period of time to meet

all regulatory requirements, including those of the hospital or institution.

Additional requirements for record retention are those required by the Food and Drug Administration for studies conducted under IND. The investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

To fulfill requirements of the National Institutes of Health, grantees must retain the records pertinent to all studies supported by the award for three years from the date the final Federal Financial Report is submitted to NIH.

7.5 Protocol Deviations

The following protocol deviations will be recorded and summarized in the final report:

1) eligibility (inclusion/exclusion) violations,
2) study drug dosing violations,
3) excluded medication violations,
4) procedures performed outside the protocol-specified window,
5) procedures not done,
6) subject non-compliance and
7) other, to be specified by the Investigator.

8. Human Subjects

8.1 GCP Statement

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

8.2 Benefits

The potential benefits of this study are: Severe osteogenesis imperfecta is both debilitating and progressive, and, as discussed previously, treatment options for adults with severe OI are limited. This work will have a direct impact on the treatment of these patients if it is found that therapy to decrease TGFβ activity in humans with severe OI is safe and has beneficial effects on bone as assessed by biochemical markers and a BMD. If successful, such therapy may be of significant benefit in reducing the fracture rates and pain, and improving the quality of life of individual study participants. In addition, participants will have access to routine medical care and follow-up.

Severe osteogenesis imperfecta not only takes its toll on individuals who have the disease, but it also impacts society as a whole through the devastating loss of human potential resulting from the disorder. In addition, medical care for a person with type III or IV OI requires a variety of interventions, many of which are expensive and place an increased burden on our already overextended health care system. This phase I clinical trial should provide important information about a possible new therapy for patients with OI. If successful, such therapy may be of significant benefit in reducing the morbidity and improving the quality of life in these patients. As well as reducing the suffering of

those with the most severe forms of OI, a beneficial therapy might decrease the frequency of medical interventions now required to manage the disease. No matter what the outcome of the trial, the information to be learned could be useful in optimizing therapy and clinical management of patients with this disorder.

8.3 Risks

The potential risks of this study are:

Blood samples will be drawn for safety labs. It is expected that there may be bruising and mild discomfort at the site of needle insertion when phlebotomy is performed. Fainting may even occur.

Participants will be exposed to radiation during dual-energy X-ray absorptiometry scanning and radiographs. The total amount of radiation that the participant will receive in this study is about 1.1 mSv or 110 mrem, and is approximately equivalent to a uniform whole body exposure of 133 days of exposure to natural background radiation. (Ref http://www.doseinfo-radar.com/RADARDoseRiskCalc.html). Though the biological effects of diagnostic radiation on humans have not been studied directly, the potential risk to an individual associated with techniques used for the assessment of bone status is believed to be very small since radiation doses are low. In 2012 the United Nations Scientific Committee on the Effects of Atomic Radiation stated that for typical background radiation levels (1–13 mSv per year), it is not possible to account for any health effects.

Patients may find the pulmonary function testing, function and mobility assessments and hearing tests to be tiring.

Protection from Risk: The study will be conducted in the Clinical and Translational Science Award (CTSA) Centers or research facilities of our respective institutions comprising the BBD Consortium whenever possible. When a CTSA/research facility is not available, study visits will be conducted in the investigator's clinic.

The study implementers will be nursing staff/coordinators of the Centers with a long experience in care of individuals with OI. If any participant should incur any unexpected and untoward event during the testing procedure, the emergency caregivers, would become available on an immediate basis to provide necessary emergent management.

Female participants will have no radiographic procedures while pregnant.

8.4 Written Informed Consent

Written informed consent will be obtained from each participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and signed copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment.

Written or oral information about the study in a language understandable by the participant will be given to all participants.

8.5 Process of Consent

Consent forms will be given to potential participants prior to enrollment so that they have ample time to review the information and ask questions about the study. Forms can be mailed to the individuals in advance of their participation so that can read and ask questions before considering participating. If participation is proposed during a clinic appointment, a copy of the consent form may be sent home with the patient along with study staff contact information. Potential enrollees will be encouraged to take their time in reviewing the consent, call with questions, and contact study staff if interested in enrolling.

Anytime consent is obtained, it is incumbent on the individual obtaining the consent to ascertain whether the potential participant and his/her legal representative understand all aspects of the study. Obtaining informed consent is an unhurried, interactive process with questions asked of both the Investigator and potential participant.

For non-English speaking subjects, a translator will be available to aid in the explanation of the protocol and consent and to answer questions. A short consent form in the subject's language will be used in addition to the full English consent form.

We will follow the usual consent procedures with those 18 years and over signing consent forms. All prospective participants will be asked to sign a medical records release form along with the study consent form. Medical records may be obtained to confirm OI diagnosis and affirm that none of the exclusionary conditions are present. Results from medical history and laboratory testing may be recorded.

8.6 Certificate of Confidentiality

To help protect participant privacy, a Letter of Confidentiality has been obtained from the National Institutes of Health (NIH). With this Certificate, the researchers cannot be forced to disclose information that may identify a study participant, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify a participant, except as explained below.

The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed to meet the requirements of the federal Food and Drug Administration (FDA).

Even with the Certificate of Confidentiality, the investigators continue to have ethical obligations to report child abuse or neglect and to prevent an individual from carrying out any threats to do serious harm to themselves or others. If keeping information private would immediately put the study participant or someone else in danger, the investigators would release information to protect the participant or another person.

Department of Health and Human Services (DHHS) personnel may request identifying

information for purposes of performing audits, carrying out investigations of DHHS grant recipients, or evaluating DHHS funded research projects.

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